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Cyclophosphamide versus methylprednisolone for treating neuropsychiatric involvement in systemic lupus erythematosus (Review)

Fernandes Moça Trevisani V, Castro AA, Ferreira Neves Neto J, Atallah ÁN

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[Intervention Review]

Cyclophosphamide versus methylprednisolone for treating neuropsychiatric involvement in systemic lupus erythematosus

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ABSTRACT

Background

Neuropsychiatric involvement in systemic lupus erythematosus (SLE) is complex and it is an important cause of morbidity and mortality. Management of nervous system manifestations of SLE remains unsatisfactory. This is an update of a Cochrane review first published in 2000 and previously updated in 2006.

Objectives

To assess the benefits and harms of cyclophosphamide and methylprednisolone in the treatment of neuropsychiatric manifestations of SLE.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, LILACS, SCOPUS and WHO up to and including June 2012. We sought additional articles through handsearching in relevant journals as well as contact with experts. There were no language restrictions.

Selection criteria

We included all randomised controlled trials that compared cyclophosphamide to methylprednisolone in patients with SLE of any age and gender and presenting with any kind of neuropsychiatric manifestations.

Data collection and analysis

Two review authors independently extracted, assessed and cross-checked data. We produced a 'Summary of findings' table. We presented dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs).

Main results

We did not include any new trials in this update. One randomised controlled trial of 32 patients is included. Concerning risk of bias, generation of the allocation sequence was at low risk; however, allocation concealment, blinding and selective reporting were at high risk. Treatment response, defined as 20% improvement from basal conditions by clinical, serological and specific neurological measures, was found in 94.7% (18/19) of patients using cyclophosphamide compared with 46.2% (6/13) in the methylprednisolone group at 24 months (RR 2.05, 95% CI 1.13 to 3.73). This was statistically significant and the number needed to treat for an additional beneficial outcome (NNTB) of

treatment response is three. We found no statistically significant differences between the groups in damage index measurements (Systemic Lupus International Collaborating Clinics (SLICC)). The median SLE Disease Activity Index (SLEDAI) rating favoured the cyclophosphamide group. Cyclophosphamide use was associated with a reduction in prednisone requirements. All the patients in the cyclophosphamide group had electroencephalographic improvement but there was no statistically significant difference in decrease between groups in the number of monthly seizures. No statistically significant differences in adverse effects, including mortality, were reported between the groups.

Authors' conclusions

This systematic review found one randomised controlled trial with a small number of patients in the different clinical subgroups of neurological manifestation. There is very low-quality evidence that cyclophosphamide is more effective in reducing symptoms of neuropsychiatric involvement in SLE compared with methylprednisolone. However, properly designed randomised controlled trials that involve large numbers of individuals, with explicit clinical and laboratory diagnostic criteria, sufficient duration of follow-up and description of all relevant outcome measures, are necessary to guide practice. As we did not find any new trials to include in this review at update, the conclusions of the review did not change.

PLAIN LANGUAGE SUMMARY

Cyclophosphamide versus methylprednisolone for lupus

Does cyclophosphamide work to treat central nervous system lupus (neuropsychiatric lupus)?

Researchers in The Cochrane Collaboration conducted a review of the effect of cyclophosphamide for people with central nervous system lupus compared to the usual treatment of methylprednisolone. After searching for all relevant studies, they found one study with 32 people. The study compared people who took cyclophosphamide by IV (intravenous or through a vein) to people who took steroids (methylprednisolone by IV). All people took steroid pills (prednisone) at the beginning of the study and the amount was decreased over the study. The study lasted two years.

Their findings are summarised below:

In people with central nervous system lupus:

- We are uncertain whether cyclophosphamide improves signs and symptoms or disease activity compared to methylprednisolone.

- No differences between the two groups were found in tissue or organ damage, or in the number of monthly seizures, but this may have happened by chance.

- After six months of treatment, people who took cyclophosphamide took fewer prednisone pills than people who took methylprednisolone.

- And at the end of two years, more people who took cyclophosphamide stayed on their treatment than people who took methylprednisolone.

We often do not have precise information about side effects and complications. This is particularly true for rare but serious side effects. Side effects, such as infections, high blood sugar and high blood pressure, pancreas problems and death occurred about the same amount in people who took cyclophosphamide or methylprednisolone.

What is central nervous system lupus and how could cyclophosphamide help?

Systemic lupus erythematosus (SLE) is a disease in which the body's immune system attacks the body. In CNS lupus (central nervous system lupus) the body may have attacked and damaged the cells in the brain and spine. This damage may cause a person to have convulsions/seizures, chronic headaches, confusion and psychosis. Drugs such as corticosteroids (prednisone or methylprednisolone) are usually used for lupus to decrease inflammation and control the immune system. Immunosuppressive agents or cytotoxics such as cyclophosphamide (CTX or Cytoxan) may also be used.

What happens to people with central nervous system lupus who take cyclophosphamide compared to methylprednisolone?

- 49 more people who took cyclophosphamide improved than people who took methylprednisolone.

- 95 out of 100 people had at least a 20% improvement in symptoms with cyclophosphamide.

- 46 out of 100 people had at least a 20% improvement in symptoms with methylprednisolone.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Cyclophosphamide versus methylprednisolone for treating neuropsychiatric involvement in systemic lupus erythematosus

Cyclophosphamide versus methylprednisolone for treating neuropsychiatric involvement in systemic lupus erythematosus

Patient or population: patients with neuropsychiatric involvement in systemic lupus erythematosus
Settings: two tertiary care centres in Mexico City
Intervention: cyclophosphamide

Comparison: methylprednisolone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control (Methylprednisolone)	Cyclophosphamide				
Response to treatment (20% improvement)* Follow-up: mean 24 months	**462 per 1000**	**947 per 1000** (522 to 1000)	**RR 2.05** (1.13 to 3.73)	32 (1 study)	⊕⊖⊖⊖ **very low** [1,2,3]	Absolute risk difference 49% (95% CI 20% to 77%) Relative per cent change 105% (95% CI 13% to 273%) NNTB 3 (95% CI 2 to 6)
Adverse events - Urinary tract infections Follow-up: mean 24 months	**615 per 1000**	**529 per 1000** (289 to 966)	**RR 0.86** (0.47 to 1.57)	32 (1 study)	⊕⊖⊖⊖ **very low** [1,2,3]	Absolute risk difference -90% (95% CI -44% to 26%) Relative per cent change -14% (95% CI -53% to 57%) Not statistically significant
Adverse events - Death Follow-up: mean 24 months	**231 per 1000**	**531 per 1000** (7 to 453)	**RR 0.23** (0.03 to 1.96)	32 (1 study)	⊕⊖⊖⊖ **very low** [1,2,3]	Absolute risk difference -18% (95% CI -43% to 7%) Relative per cent change -77% (95% CI -97% to 96%)

						Not statistically significant
SLICC scores (damage index) Scale: from 0 to 48 (lower is better) Follow-up: mean 12 months	See comment	See comment	Not estimable	32 (1 study)	⊕⊝⊝⊝ **very low** [1,2,3]	Available data (medians and ranges) could not be transformed to permit analysis. No significant differences between the groups were found in SLICC measurements.
SLEDAI scores (disease activity index) Scale: from 0 to 106 (lower is better) Follow-up: mean 12 months	See comment	See comment	Not estimable	32 (1 study)	⊕⊝⊝⊝ **very low** [1,2,3]	Available data (medians and ranges) could not be transformed to permit analysis. The median SLEDAI rating favoured the cyclophosphamide group.
Prednisone sparing Follow-up: mean 15 months	See comment	See comment	Not estimable	32 (1 study)	⊕⊝⊝⊝ **very low** [1,2,3]	Available data (medians and ranges) could not be transformed to permit analysis. Cyclophosphamide use was associated with reduction of prednisone requirements by the 6th month of treatment.
Seizures Follow-up: mean 24 months	**333 per 1000**	**856 per 1000** (306 to 1000)	**RR 2.57** (0.92 to 7.14)	11 (1 study)[4]	⊕⊝⊝⊝ **very low** [1,2,3]	Absolute risk difference 67 % (95% CI 2 5 % to 1 08 %) Relative percent change 157 % (95% CI -8% to 614 %) Not statistically significant

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **NNTB:** number needed to treat for an additional beneficial outcome; **RR:** risk ratio; **SLEDAI:** Systemic Lupus Erythematosus Disease Activity Index; **SLICC:** Systemic Lupus International Collaborating Clinics

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

*Response to treatment = 20% improvement from basal conditions on clinical, laboratory or specific neurological testing variables.
[1]The study had adequate sequence generation, but the allocation concealment was not considered to be adequate. Blinding was not reported. Incomplete data were not addressed adequately. The study was not considered to be free from other bias as only 32 patients were randomised in blocks of 10 and the trial stopped recruiting early due to apparent benefit.
[2]The 95% confidence interval around the effect estimate is wide and includes both the possibility of significant benefit and harm of intervention.

[3]Only one study was included.
[4]Only a subgroup of 11 participants in the study had seizures.

BACKGROUND

Description of the condition

Neuropsychiatric involvement in systemic lupus erythematosus (SLE) is complex and several clinical presentations are related to this disease, including seizures, chronic headache, transverse myelitis, cerebrovascular disease, psychosis, movement disorders, psychiatric disorders, cranial neuropathy, acute confusional state and cognitive dysfunction. The incidence of neuropsychiatric events ranges from 13% to 60% and the incidence of mortality related to neuropsychiatric involvement ranges from 7% to 13% (Gladman 1994; Sibley 1992).

Factors related to the pathological mechanisms of neuropsychiatric involvement in SLE are: autoantibodies such as antiphospholipids, lymphotoxins, antineural and cytoplasmic membrane as the anti-ribosomal P, antineurofilament, anti N-methil-D-aspatate (NMDA) receptor subunit NR2 and high levels of cytokines as alpha interferon and interleukin 6 (IL-6) (Bertsias 2010; Bonfa 1987; Boumpas 1995; Denburg 1994; Gladman 1994; Gono 2011; Gono 2011; Sibley 1992; Urowitz 1980). As there are no laboratory tests or imaging examinations specific to neuropsychiatric lupus activity, elucidation of the pathogenesis is difficult (Bertsias 2010; Boumpas 1995; Denburg 1995; Gladman 1994; Sibley 1992; Urowitz 1980). It is also difficult to attribute clinical manifestations, as there are frequently doubts related to the presence of infection, metabolic and endocrine disturbances or adverse effects of medicines (Bertsias 2010).

Description of the intervention

Treatment depends on establishing the diagnosis, the seriousness of the clinical manifestations and also on whether the underlying process is inflammatory, thrombotic or both. Methylprednisolone is widely used for the treatment of almost all types of lupus activity manifestation. Several reviews have demonstrated the effectiveness of methylprednisolone, although neuropsychiatric involvement has not been the main focus. There is controversy as to whether the use of corticoids causes or exacerbates psychotic manifestations (Denburg 1994; Eyanson 1980; Wolkowitz 1990). The use of cyclophosphamide is established for lupus nephritis, but not for neuropsychiatric involvement in SLE (Austin 1986; Felson 1984; Steinberg 1991).

How the intervention might work

Humoral immune responses are exacerbated in SLE, with autoantibody production, immune complex formation and tissue injury. Corticosteroids are immunosuppressive drugs and cyclophosphamide is a cytotoxic drug that suppresses cellular and humoral immune response. The aim of immunosuppressive drugs is to suppress the primary humoral immune response and prevent tissue damage (Aranow 2008).

Why it is important to do this review

This systematic review summarises the evidence from controlled trials for the effectiveness and safety of cyclophosphamide in the treatment of neuropsychiatric manifestations of lupus. It has been updated previously in 2006and this is the current update.

OBJECTIVES

To assess the benefits and harms of cyclophosphamide compared to methylprednisolone in the treatment of neuropsychiatric involvement in systemic lupus erythematosus.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials addressing the therapeutic clinical question, in any language, irrespective of publication date.

Types of participants

Patients of any age or gender who fulfil the criteria of the American Rheumatology Association for the diagnosis of systemic lupus erythematosus (Tan 1982) and who present one of the following neuropsychiatric events: psychosis; visual or auditory hallucination; delirium; illogical thoughts and disturbance of behaviour; depression; headache; seizures; organic brain syndrome (delirium, stupor and coma); cranial neuropathy (blindness, palpebral ptosis, facial paralysis); ischaemic and haemorrhagic cerebral vascular disease; transverse myelitis; mononeuritis (single or multiplex); polyneuropathy; autonomic disorder; myasthenia gravis; demyelinating syndrome; aseptic meningitis and myelopathy disorder.

Types of interventions

Patients who received cyclophosphamide for the treatment of neuropsychiatric manifestations compared with patients who received methylprednisolone, irrespective of dose.

Types of outcome measures

Major outcomes

We included the following major clinical outcome measures for potential analysis.

Effectiveness

- Response to treatment through clinical evaluation of muscular strength, motor disabilities, neuromuscular reflexes, persistence of seizure activity and usage of adequate scales of evaluation of neurocognitive dysfunction (mini mental state examination - MMSE), depression (Hamilton Rating Scale for Depression - HDRS) and appraisal of psychotic symptoms (Brief Psychiatric Rating Scale (BPRS), Positive and Negative Syndrome Scale (PANSS)) or equivalent and specific neurological measures (evoked potentials, cerebrospinal fluid analysis, electromyography, magnetic resonance imaging and electroencephalogram evaluation).
- Damage assessment by Systemic Lupus International Collaborating Clinics (SLICC) scores.
- Global activity by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).
- Prednisone sparing.
- Seizures.

Safety

- Adverse events (infections, hypertension, hyperglycaemia, alopecia) and overall mortality (patients who died during the entire period of treatment).

Minor outcome

- Adherence to treatment.

Search methods for identification of studies

The Trials Search Co-ordinator of the Cochrane Musculoskeletal Group searched for any trials or references to relevant trials (published, in press or in progress). All publications were sought through computerised searches in the following electronic databases: the Cochrane Central Register of Controlled Clinical Trials (CENTRAL) (Appendix 1) (2012, Issue 5), MEDLINE (1966 to 1 June 2012) (Appendix 2), EMBASE (1982 to 1 June 2012) (Appendix 3), LILACS (1982 to 1 June 2012) (Appendix 4), Scopus (2005 to 13 June 2012) (Appendix 5), World Health Organization International Clinical Trials Registry Platform http://www.who.int/ictrp/en/ (1 June 2012) (Appendix 6) and by checking reference lists. We sought additional articles through handsearching in relevant journals as well as contact with experts. There were no language restrictions. There were no limits on language or date, or any other restrictions.

Data collection and analysis

Selection of studies

Two review authors independently assessed the titles and abstracts of all reports. We obtained full-text hard copies for studies that met the selection criteria. Two review authors (VFMT, RM) selected trials to be included in this update of the review. We resolved disagreements by consensus.

Data extraction and management

The review authors independently extracted and cross-checked data. There was no disagreement between the authors of this review. We summarised the results of each trial on an intention-to-treat basis in 2 x 2 tables for each outcome. We assessed the trial's external validity by analysis of: (a) PARTICIPANTS: inclusion, exclusion and diagnostic criteria, male and female, age, number of participants, and we analysed the sample size and power calculation; (b) INTERVENTIONS: besides the types of interventions described above we also assessed route of administration, dosage and duration; (c) OUTCOMES (also described above).

Assessment of risk of bias in included studies

The same review authors independently assessed the risk of bias for each trial using The Cochrane Collaboration's 'Risk of bias' tool (Higgins 2011). We recorded details of randomisation (sequence number, allocation concealment), blinding, incomplete outcome data, selective outcome reporting and other sources of bias such as blocked randomisation. Each review author classified each of these domains as: 'Low risk' of bias, 'High risk' of bias or 'Unclear risk' of bias, according to The Cochrane Collaboration 'Risk of bias' tool (Higgins 2011).

Measures of treatment effect

If appropriate, we had planned to subgroup the studies for meta-analysis according to the analysis of the items above and their clinical homogeneity, with a fixed-effect model and 95% confidence intervals (CIs). We performed the analysis using risk ratios (RRs) and 95% CIs for dichotomous outcomes, and mean differences (MDs) and 95% CIs for continuous outcomes (reporting mean and SD or standard error (SE) of the mean).

Unit of analysis issues

The unit of analysis was individual patients.

Dealing with missing data

We did not contact investigators to request missing data because we did not think it was necessary.

Assessment of heterogeneity

We planned to use the I^2 statistic to measure heterogeneity in the results of the trials. We considered substantive heterogeneity to be an I^2 value above 50%, according to the criteria below. Thresholds for the interpretation of I^2 can be misleading, since the importance of inconsistency depends on several factors. A rough guide to interpretation is as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity*;
- 50% to 90%: may represent substantial heterogeneity*;
- 75% to 100%: considerable heterogeneity*.

*The importance of the observed value of I^2 depends on (i) the magnitude and direction of effects and (ii) the strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or a confidence interval for I^2).

Assessment of reporting biases

During the assessment of reporting bias we considered all domains defined in Chapter 10 of *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) including:

- publication bias;
- time lag bias;
- multiple (duplicate) bias;
- location bias;
- citation bias;
- language bias;
- outcome reporting bias.

Data synthesis

We planned to summarise all data in a meta-analysis, according to the availability of data, with a random-effects model. For non-parametric data we intended to synthesise results in tables.

Subgroup analysis and investigation of heterogeneity

We pre-specified three possible reasons for heterogeneity: (a) that response differs according to the difference in the quality of the trial; (b) that response differs according to the sample size; (c) that response differs according to clinical heterogeneity. We planned to assess these by looking at separate subgroups of trials. Clinical heterogeneity would be assessed by clinical experts. However, since only one trial was found which met the inclusion criteria, heterogeneity was not an issue in this review

Sensitivity analysis

When indicated we planned to undertake sensitivity analyses to determine if the results or conclusions were affected or not during the review process. For this analysis we considered the following features of study methodological quality: allocation concealment, blinding of participants and assessors and intention-to-treat analysis.

'Summary of findings' table and grading of the evidence

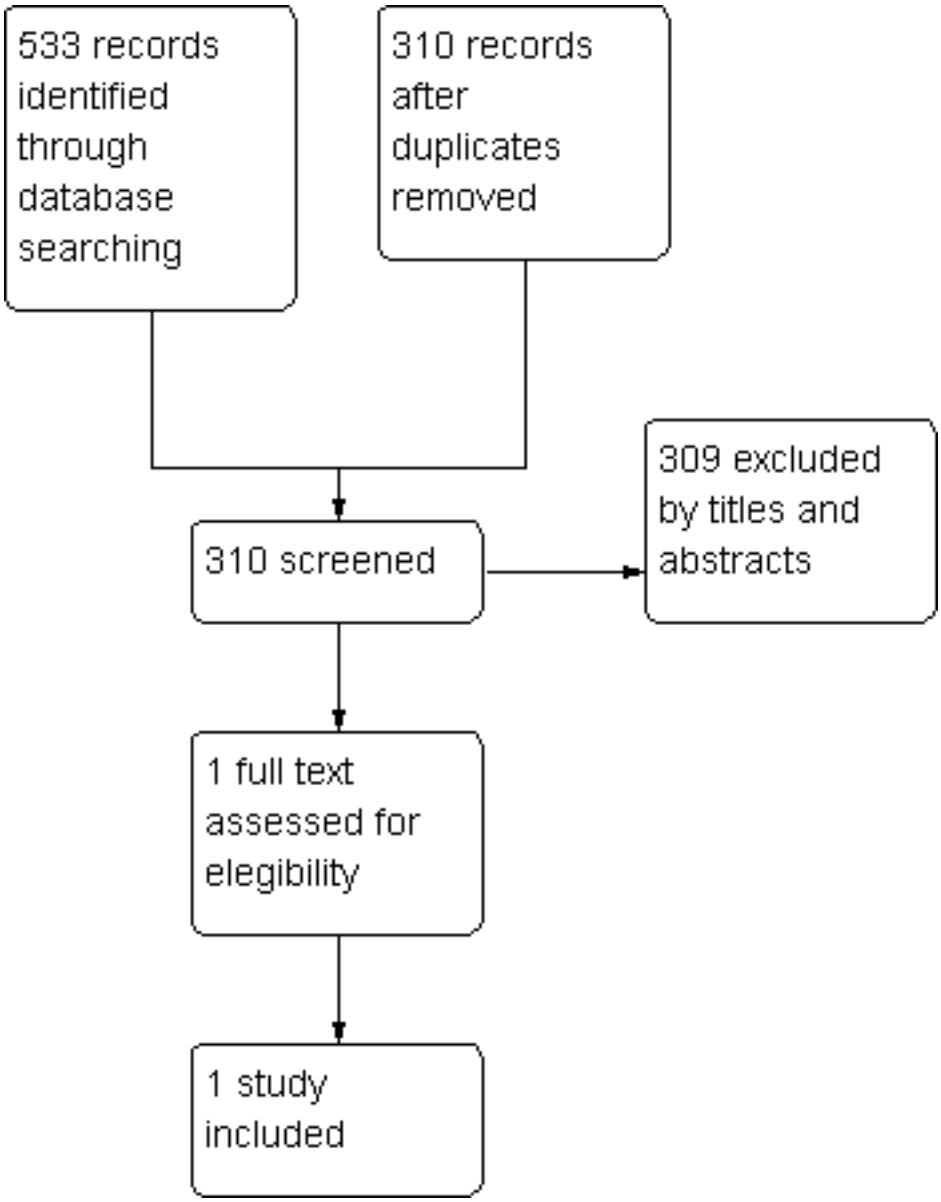
We provide a list of important outcomes in the 'Summary of findings' table, with the number of participants and the magnitude of effects. We graded the quality of evidence using the GRADE approach (Schünemann 2011). The outcomes used in the 'Summary of findings' table are: response to treatment, SLICC scores, SLEDAI, prednisone sparing, seizures, adverse events and mortality.

RESULTS

Description of studies

We identified 533 records through database searching. After removing duplicates we screened 310 records (Figure 1). We found 25 RCTs that used different interventions for SLE manifestations: 14 out of the 25 referred only to renal complications, not mentioning other clinical manifestations or not giving data on them, which made data collection impossible. Of the 11 remaining studies, one was a protocol (Euler 1991), one did not provide data on neuropsychiatric involvement, four only included patients taking cyclophosphamide in different regimens and only laboratory findings were analysed, and three studies included patients with systemic manifestations, but these were excluded because data for neuropsychiatric involvement were not available in a suitable form for analysis. See Characteristics of excluded studies table.

Figure 1. Study flow diagram.



One study met the inclusion criteria (Barile-Fabris 2005). This study included 32 patients aged over 18 years old with active neurological involvement in systemic lupus erythematosus manifestations. Each patient was allocated to receive methylprednisolone 1 g daily for 3 days as induction treatment. This was then followed by one of the following two treatments: methylprednisolone 1 g for three days monthly for four months, then bimonthly for six months and then every three months for one year, or cyclophosphamide 0.75 g/m^2 body surface monthly for one year and then every three months for another year. Oral prednisone was started on the fourth day of treatment, at 1 mg/kg/day, for no more than three months and tapered according to disease activity/remission. See Characteristics of included studies table.

Risk of bias in included studies

Two review authors (VFMT, RM) evaluated the methodological quality of the selected study independently using The Cochrane Collaboration's tool for assessing risk of bias. In the included trial (Barile-Fabris 2005) the allocation sequence was adequately generated; however, the allocation sequence could be foretold by investigators since the list and the operative manuals were distributed to both centres. The allocation was probably not concealed because the dosing schedule was different between groups. It is not mentioned whether blinding of participants, providers and outcome assessors was done. There is insufficient information to permit judgement of all domains of reporting bias (publication bias, time lag bias, multiple (duplicate) bias, location bias, citation bias, language bias and outcome reporting bias). However, concerning selective outcome reporting, all the outcomes listed in the methods section of the paper are reported in the results section. In addition we did not consider the study to be free from other bias as only 32 patients were randomised in blocks of 10 at two centres (Figure 2; Figure 3).

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

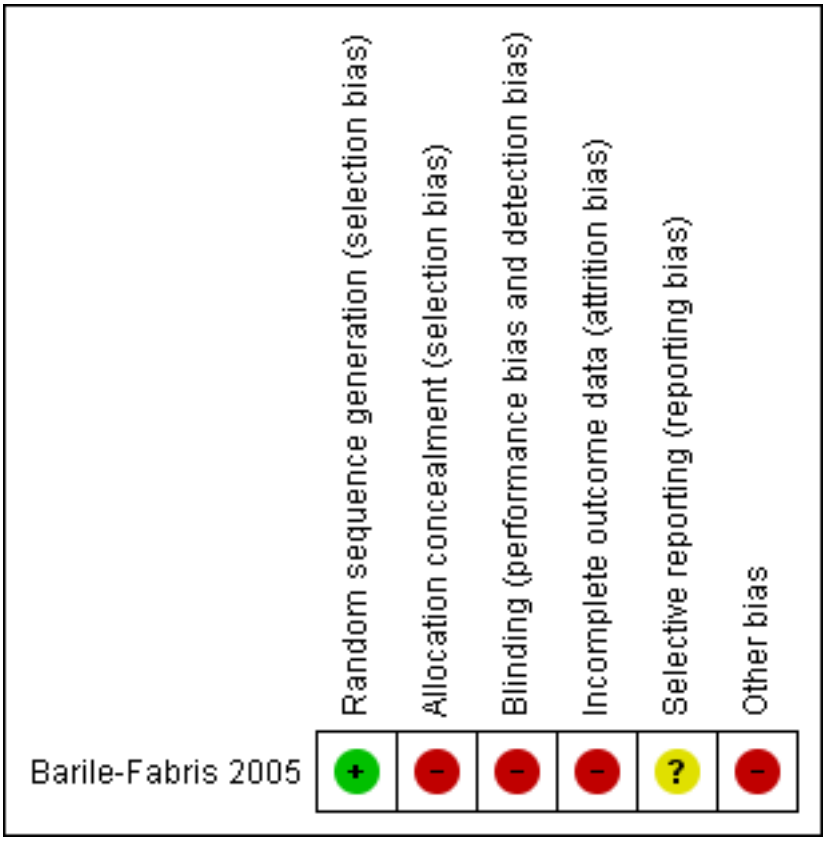
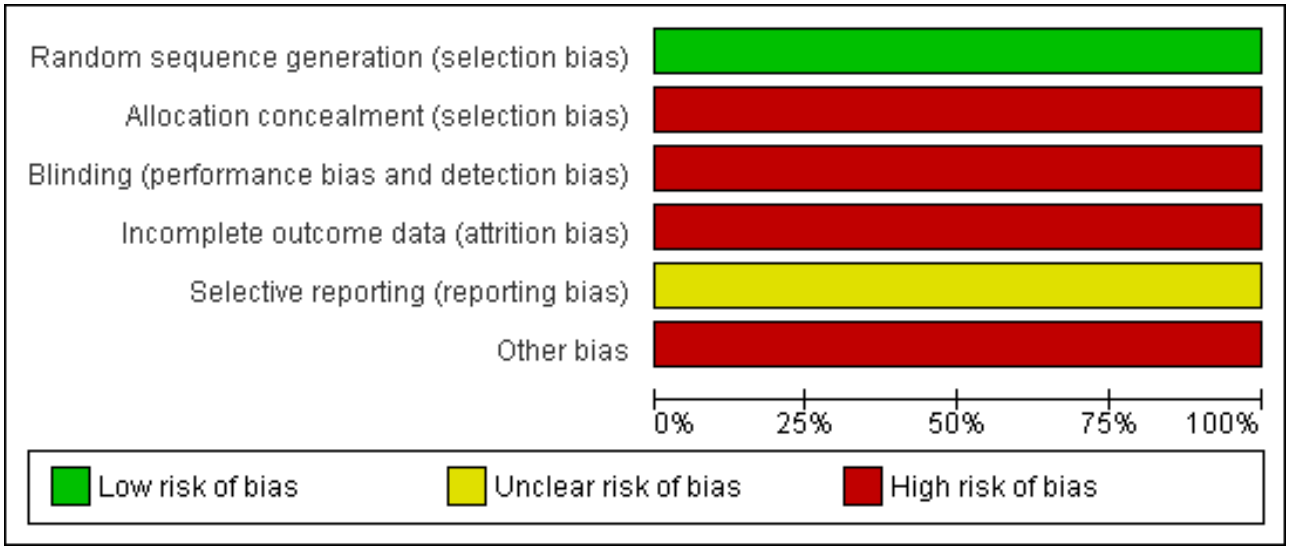


Figure 3. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Effects of interventions

See: **Summary of findings for the main comparison** Cyclophosphamide versus methylprednisolone for treating neuropsychiatric involvement in systemic lupus erythematosus

Only one randomised controlled trial was included in this review (Barile-Fabris 2005). The timing of the assessment of all outcomes reported in this study was at two years.

Effectiveness

Overall, the response rate, defined according to Neuwelt et al as at least a 20% improvement from basal conditions by clinical, serological and specific neurological measures, was 75% (24/32 patients) (Barile-Fabris 2005). A statistically significant greater number of people responded to treatment in the cyclophosphamide group. Treatment response was found in 94.7% (18/19) of patients using cyclophosphamide compared with 46.2% (6/13) in the methylprednisolone group at 24 months (risk ratio (RR) 2.05, 95% confidence interval (CI) 1.13 to 3.73) (Analysis 1.1). The number needed to treat for an additional beneficial outcome (NNTB) of treatment response is three.

Motor and psychiatric deficit was not measured in the study.

No statistically significant differences between the groups were found in Systemic Lupus International Collaborating Clinics (SLICC) measurements (Analysis 1.2).

The median Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) rating favoured the cyclophosphamide group after 12 months of follow-up (cyclophosphamide 1 (range 0 to 5) versus methylprednisolone 4 (range 0 to 30) (P = 0.007) (Analysis 1.3).

Cyclophosphamide use was associated with reduction in prednisone requirements by the sixth month of treatment (cyclophosphamide 15 mg/day (range 10 to 35); methylprednisolone 27 mg/day (5 to 45), P = 0.001) (Analysis 1.4).

All the patients in the cyclophosphamide group had electroencephalographic improvement, but there was no statistically significant decrease between groups in the number of monthly seizures (RR 2.57, 95% CI 0.92 to 7.14) (Analysis 1.5).

Safety

There were no statistically significant differences in adverse events, such as infection rate, systemic hypertension, hyperglycaemia and pancreatitis, between the groups (Analysis 1.6).

Although mortality was not planned as an outcome by authors of the primary study, we considered it in this review and it was available in the results section of the trial. No statistically significant difference in deaths was observed between groups (RR 0.23, 95% CI 0.03 to 1.96) (Analysis 1.6).

It was not possible to extract more data from the study because there were small numbers of patients in the clinical subgroups of neurological manifestation and the authors did not provide sufficient information to allow data extraction.

A 'Summary of findings' table summarises these results (see Summary of findings for the main comparison).

Adherence to treatment

There was a trend in favour of the cyclophosphamide group in completion of the protocol (up to two years of treatment), though this was not statistically significant (RR 2.74, 95% confidence interval 0.96 to 7.82) (Analysis 1.7).

DISCUSSION

Summary of main results

Our results demonstrate a statistically significant effect of cyclophosphamide in terms of treatment response, defined as a 20% improvement of basal condition. There was no difference between the groups in the SLICC damage index, however there was a statistically significant difference favouring cyclophosphamide in relation to the activity index (SLEDAI). The daily requirement

for prednisone decreased significantly in the cyclophosphamide group. All the patients in the cyclophosphamide group had electroencephalographic improvement and the number of monthly seizures decreased, however this was not statistically significant. No statistically significant difference was observed between the two treatment groups in relation to adverse events and mortality.

Overall completeness and applicability of evidence

A number of randomised controlled trials in systemic lupus erythematosus (SLE) are restricted to renal involvement. Neuropsychiatric involvement has been neglected in trials. In the few studies that included systemic manifestations, there is a lack of clarity in the definition of outcomes and lack of available data means that interpretation is difficult. As these trials are also of insufficient quality and have small sample sizes, they do not enable any valid conclusions about neuropsychiatric involvement in SLE. This review has highlighted the inadequacy of research in the area of neuropsychiatric involvement in SLE. For clinical practice it is necessary to consider both the benefits and harms of the interventions.

Quality of the evidence

As can be seen from the 'Summary of findings' table, the quality of the evidence was very low. The one included study had adequate sequence generation, but we did not consider allocation concealment to be adequate. Blinding was not reported and could not have taken place, at least not for personnel, as dosing schedules for the two interventions were different. Incomplete outcome data were not balanced between groups and therefore we considered this a high risk of bias. It was unclear whether the study was free from selective outcome reporting, however all listed outcomes were reported. In addition, we did not consider the study to be free from other bias as only 32 patients were randomised in blocks of 10 at two centres, which could have led to bias.

Potential biases in the review process

We carried out an exhaustive search so we would expect that no studies were missed. We performed double data extraction to minimise potential biases. A strong point of the review process is that there were no disagreements between the authors regarding the data extraction from the study.

Agreements and disagreements with other studies or reviews

The results of this systematic review agree with the findings of the included study, since there are a limited number of clinical trials in this specific area. The present study is the only randomised controlled trial which considers neuropsychiatric involvement in SLE. There are no other systematic reviews with which we can compare outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

We found one randomised controlled trial which has some limitations, such as the small number of patients in the different clinical subgroups of neurological manifestation. Multicentre, methodologically rigorous trials are needed, but it is necessary to understand the different pathogenic mechanisms involved in central nervous system lupus and to develop a clinically rational approach when proposing clinical trials and assessing the efficacy of the various therapeutic interventions. It seems that cyclophosphamide is more effective in the treatment of neuropsychiatric involvement in systemic lupus erythematosus compared with methylprednisolone, but caution is needed in interpreting this result as the quality of the evidence was rated as very low for the outcomes of interest.

Implications for research

Properly designed randomised controlled trials, which involve large, representative numbers of individuals, with explicit clinical and laboratory diagnostic criteria, sufficient duration of follow-up and description of all relevant outcome measures, are necessary to guide practice.

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REFERENCES

References to studies included in this review

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Barile-Fabris 2005

Methods	Generation of allocation sequence: computer-generated program Allocation concealment: not reported Blinding: not reported Characteristics of placebo: not used Sample size calculation: not reported Number of patients randomised: 32 Loss to follow-up: 16 patients Intention-to-treat analysis: yes Similarity between groups: yes
Participants	Inclusion criteria: Diagnosis of SLE according to the American College of Rheumatology Criteria, age > 18 years and one of the following active neurological manifestations of systemic erythematosus (NPSLE): peripheral/cranial neuropathy, optic neuritis, transverse myelitis, brainstem disease or coma. All patients were at no more than 15 days since onset. Patients with refractory seizures were also included. Exclusion criteria: Central nervous system (CNS) or systemic infections, known hypersensitivity to study drugs or metabolic encephalopathy. Patients who had received pulse methylprednisolone or cyclophosphamide at any time during the 3 months before the start of the study were also excluded. Any patients with neurological manifestations directly related to antiphospholipid syndrome were excluded, as were patients with pure psychiatric involvement. Characteristics: Group treated with cyclophosphamide: Age: 33 (17 to 48) Disease evolution in years (range): 4.2 (.11 to 16) Number of ACR criteria: 6 Basal prednisone dose (mg/day): 45 (15 to 60) Group treated with methylprednisolone: Age 26 (19 to 44) Disease evolution in years (range): 2.5 (.0 to 12) Number of ACR criteria: 6 Basal prednisone dose (mg/day): 45 (15 to 60)
Interventions	After randomisation each patient was allocated to receive methylprednisolone 1 g daily for 3 days as induction treatment. This was followed by 1 of the following 2 treatments: methylprednisolone 1 g for 3 days monthly for 4 months, then bimonthly for 6 months and then every 3 months for 1 year; or cyclophosphamide 0.75 g/m^2 body surface monthly for 1 year and then every 3 months for another year. Oral prednisone 1 mg/kg/day for no more than 3 months and tapered according to disease activity/remission.

Barile-Fabris 2005 *(Continued)*

Outcomes	(a) Improvement: 20% change from basal condition in clinical, serological and specific neurological measures (evoked potentials, cerebrospinal fluid analysis, electromyography, magnetic resonance imaging etc.) achieved by the 4th month of treatment; (b) worsening: disease progression of 20% or more despite continued treatment for at least 4 months
Notes	Setting: Mexico

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Patients were prestratified by centre and by NP manifestation and then randomised in blocks of 10 patients by a random number computer generated program." **Comment:** the sequence was adequately generated
Allocation concealment (selection bias)	High risk	**Quote:** "These lists, together with operative manuals, were distributed to both centres." **Comment:** the allocation appears not to have been concealed
Blinding (performance bias and detection bias) Objective outcomes	High risk	**Quote:** "This was followed by one of the following two treatments: MP 1 g daily for 3 days, monthly for 4 months, then bimonthly for 6 months and subsequently every 3 months for 1 year or Cy 0.75 g/m2 body surface monthly for 1 year and then every 3 months for another year. Oral prednisone was started on the fourth day of treatment, at 1 mg/kg/day, for no more than 3 months and tapered according to disease activity/remission." **Comment:** the paper provided no information on blinding participants, study personnel or outcome assessors; however, the study personnel cannot have been blinded to treatment as the dosing schedule was different between groups
Incomplete outcome data (attrition bias) All outcomes	High risk	**Quote:** "Failure to improve after 4 months was considered grounds for stopping treatment early. In which case these patients were only considered in the intention to treat analysis and were subsequently treated according to the recommendations of their attending physician."..."Fifteen patients were able to complete the protocol up to 2 years of treatment: 12 receiving Cy and only three in the MP group." **Information provided in flow diagram 1:** of the 19 people randomised to receive cyclophosphamide, 13 (68%) completed 12 months of treatment, 12 (63%) completed 24 months of treatment, 2 (11%) terminated treatment early and 2 (11%) died Of the 13 people randomised to received methylprednisolone, 3 (23%) completed 12 months of treatment, 3 (23%) completed 24 months of treatment, 6 (46%) terminated treatment early and 1 (8%) died **Comment:** from flow diagram 1, the number of people who died plus the number of people who terminated treatment early plus the number of people who completed treatment at 12 months does not equal the number of people randomised, in either group. The number of people who completed treatment at 12 and 24 months is not equal across the 2 groups.
Selective reporting (reporting bias)	Unclear risk	**Comment:** there is insufficient information to permit judgement of 'yes' or 'no'; however, all the outcomes listed in the methods section of the paper are reported in the results section

Barile-Fabris 2005 *(Continued)*

Other bias	High risk	**Quote:** "Between July 1998 and July 1999 a total of 32 patients with SLE were enrolled in the trial at two tertiary care centres in Mexico City.... Patients were prestratified by centre and by NP manifestation and then randomised in blocks of 10 patients by a random number computer generated program. " **Comment:** randomising in blocks of 10 for 32 participants at 2 centres could have led to bias (e.g. the tertiary care centre at which the patient was treated could have affected the outcome, and not just the study intervention)

ACR: American College of Rheumatology
NP: neuropsychiatric

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Austin 1986	Randomised controlled trial, but its research question is not relevant
Boumpas 1992	Randomised controlled trial, but its research question is not relevant
Cortés-Hernández 2003	Not a randomised trial
Dinant 1982	Randomisation method not stated and research question is not relevant
Donatio 1977	Randomised controlled trial, but its research question is not relevant
Edwards 1987	Randomisation method not stated; data for neuropsychiatric involvement are not available in a suitable form for analysis
Euler 1991	Only a protocol
Fries 1973	Randomisation method not stated; high loss to follow-up; data available are in an unsuitable form for analysis
Gourley 1996	Randomised, high loss to follow-up and research question is not relevant
Harisdangkul 1989	Not randomised, research question is not relevant
Kopelman 2003	Not a randomised controlled trial
Lavalle-Graef 2004	Not randomised, research question is not relevant
Lehman 2004	Not randomised, research question is not relevant
Levey 1992	Randomised, but the uses plasmaphoresis
Liebling 1982	Randomisation method not stated; research question is not relevant
Mackworth-Young 1988	Randomisation method not stated; data for neuropsychiatric involvement are not available in suitable form for analysis
Mok 2003	Not randomised
Neuwelt 1995	Not randomised

Study	Reason for exclusion
Ramos 1996	Not randomised
Sesso 1994	Randomisation method not stated; research question is not relevant
Steinberg 1971	Randomised controlled trial, but its research question is not relevant
Steinberg 1991	Randomised controlled trial, but its research question is not relevant
Stojanovich 2003	Randomisation method not stated; data for neuropsychiatric involvement are not available in a suitable form for analysis
Stratta 1992	Not randomised, data for neuropsychiatric involvement are not available in a suitable form for analysis
Yee 2003	Randomised, but data for neuropsychiatric involvement are not available

DATA AND ANALYSES

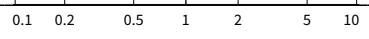
Comparison 1. Cyclophosphamide versus methylprednisolone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Response to treatment	1	32	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [1.13, 3.73]
2 SLICC			Other data	No numeric data
3 SLEDAI			Other data	No numeric data
4 Prednisone sparing			Other data	No numeric data
5 Seizures	1	11	Risk Ratio (M-H, Fixed, 95% CI)	2.57 [0.92, 7.14]
6 Adverse events	1	256	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.49, 1.28]
6.1 Urinary tract infections	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.47, 1.57]
6.2 Respiratory	1	32	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.36, 2.93]
6.3 Oropharyngeal candidiasis	1	32	Risk Ratio (M-H, Fixed, 95% CI)	3.50 [0.18, 67.45]
6.4 Herpes zoster	1	32	Risk Ratio (M-H, Fixed, 95% CI)	3.50 [0.18, 67.45]
6.5 Systemic hypertension	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.01, 5.32]
6.6 Hyperglycaemia	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.01, 5.32]
6.7 Pancreatitis	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.01, 5.32]
6.8 Death	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.03, 1.96]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Completion of the protocol after 2 years	1	32	Risk Ratio (M-H, Fixed, 95% CI)	2.74 [0.96, 7.82]

Analysis 1.1. Comparison 1 Cyclophosphamide versus methylprednisolone, Outcome 1 Response to treatment.

Study or subgroup	Cyclophosphamide n/N	Methylprednisolone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Barile-Fabris 2005	18/19	6/13		100%	2.05[1.13,3.73]
Total (95% CI)	**19**	**13**		**100%**	**2.05[1.13,3.73]**
Total events: 18 (Cyclophosphamide), 6 (Methylprednisolone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.36(P=0.02)					



Favours methylprednisolon — Favours cyclophosphamide

Analysis 1.2. Comparison 1 Cyclophosphamide versus methylprednisolone, Outcome 2 SLICC.

	SLICC			
Study	Cyclophosphamide (range)	Methylprednisolone (range)	Statistical test	P value
Barile-Fabris 2005	0.72 (0.1)	0.80 (0.1)	Mann Whitney	0.071

Analysis 1.3. Comparison 1 Cyclophosphamide versus methylprednisolone, Outcome 3 SLEDAI.

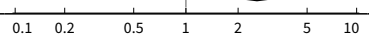
	SLEDAI			
Study	Cyclophosphamide (range)	Methylprednisolone (range)	statistical test	P value
Barile-Fabris 2005	1 (0 to 5)	4 (0 to 30)	Mann-Whitney	0,007

Analysis 1.4. Comparison 1 Cyclophosphamide versus methylprednisolone, Outcome 4 Prednisone sparing.

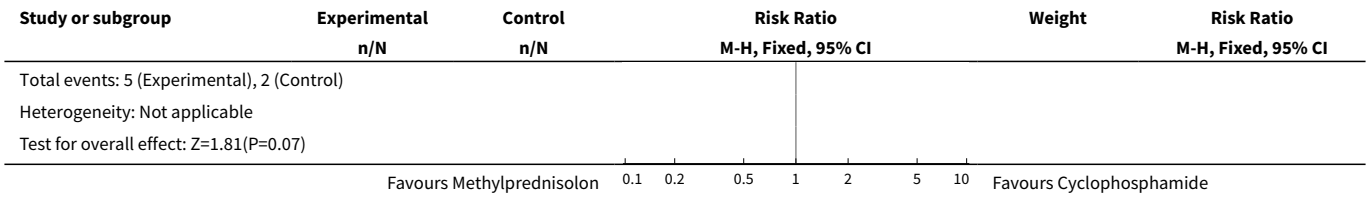
	Prednisone sparing			
Study	Cyclophosphamide (range)	Methylprednisolone (range)	Statistical test	P value
Barile-Fabris 2005	11.2 (5.20)	15.6 (5.30)	Mann Whitney	0.04*

Analysis 1.5. Comparison 1 Cyclophosphamide versus methylprednisolone, Outcome 5 Seizures.

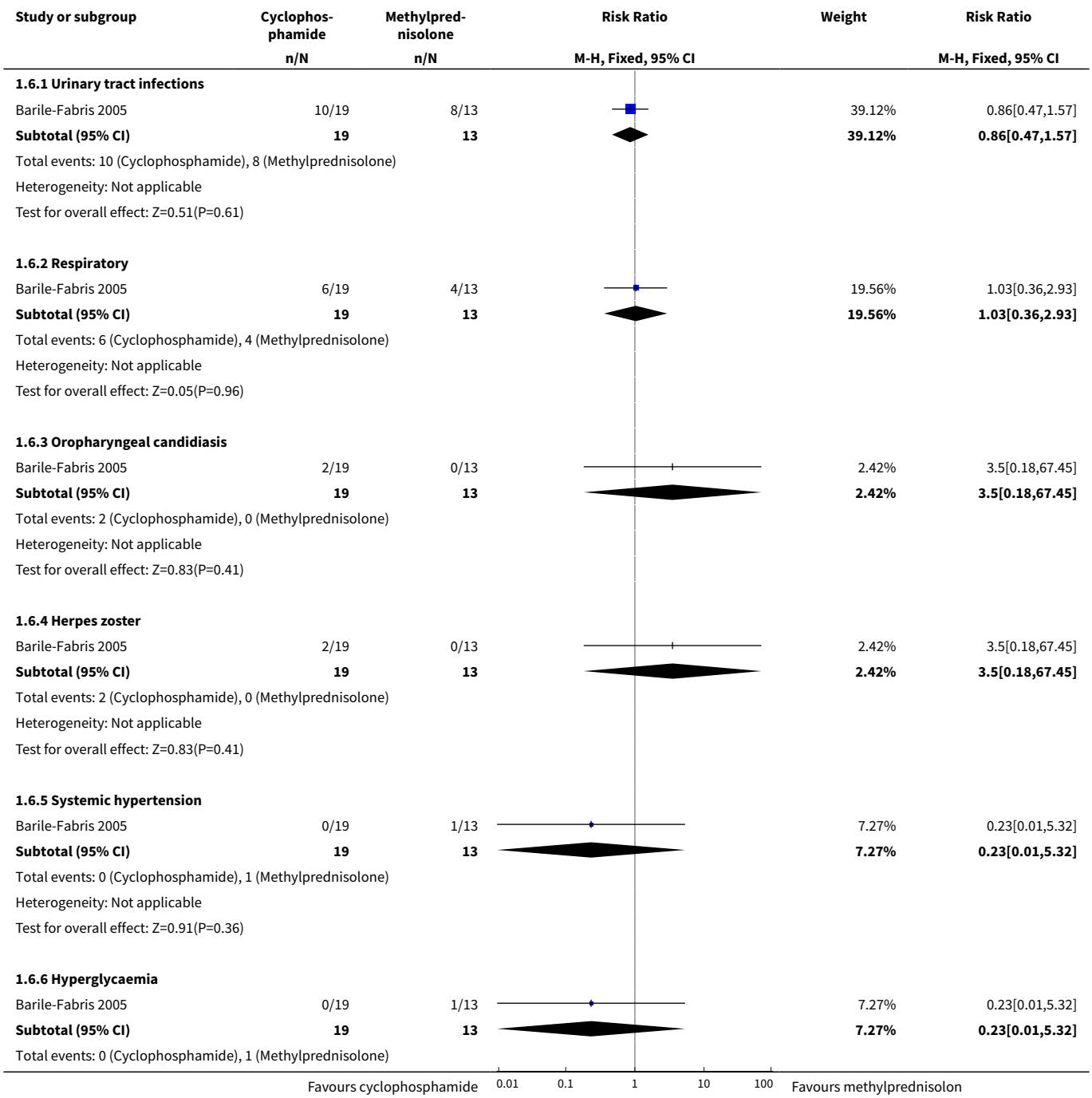
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Barile-Fabris 2005	5/5	2/6		100%	2.57[0.92,7.14]
Total (95% CI)	**5**	**6**		**100%**	**2.57[0.92,7.14]**

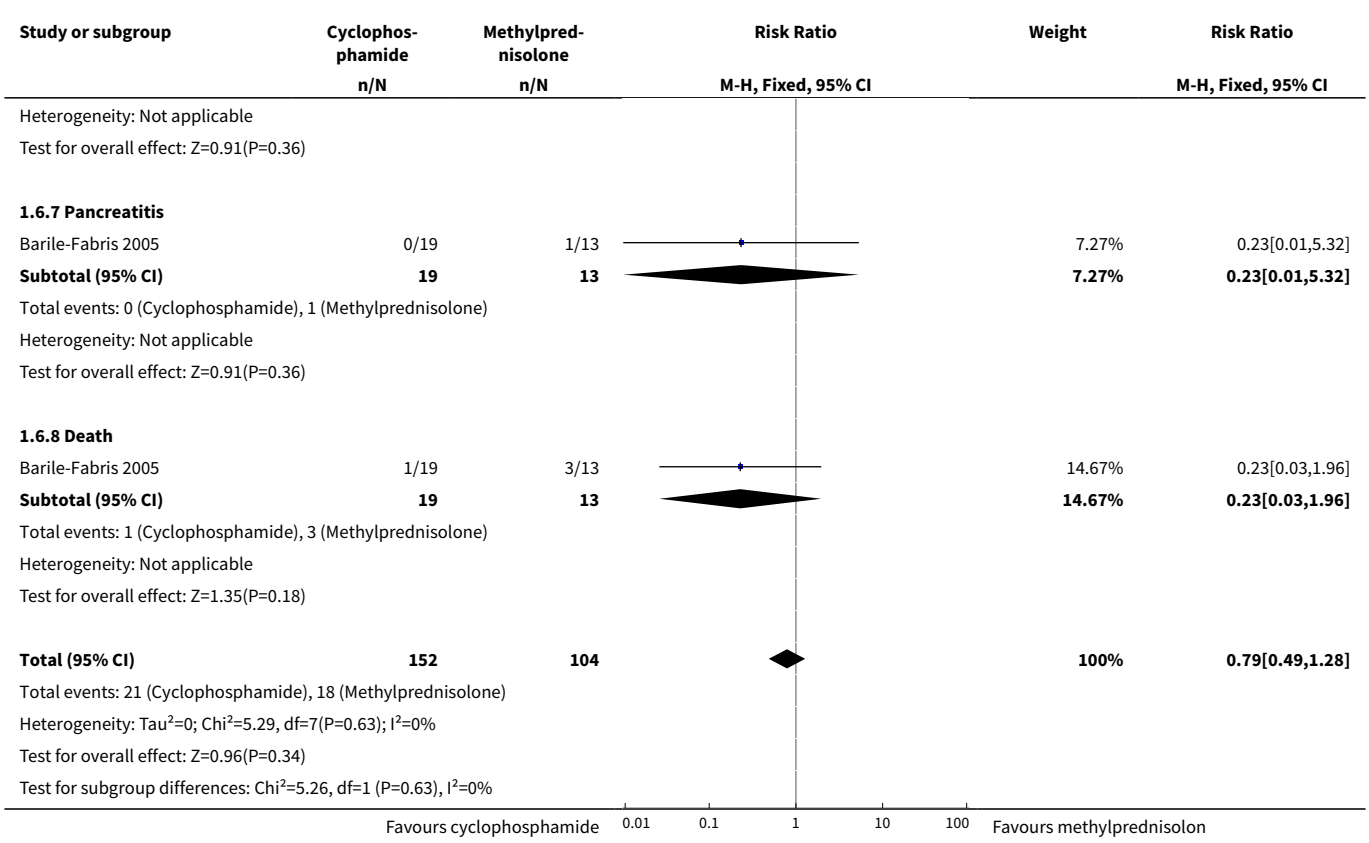


Favours Methylprednisolon — Favours Cyclophosphamide

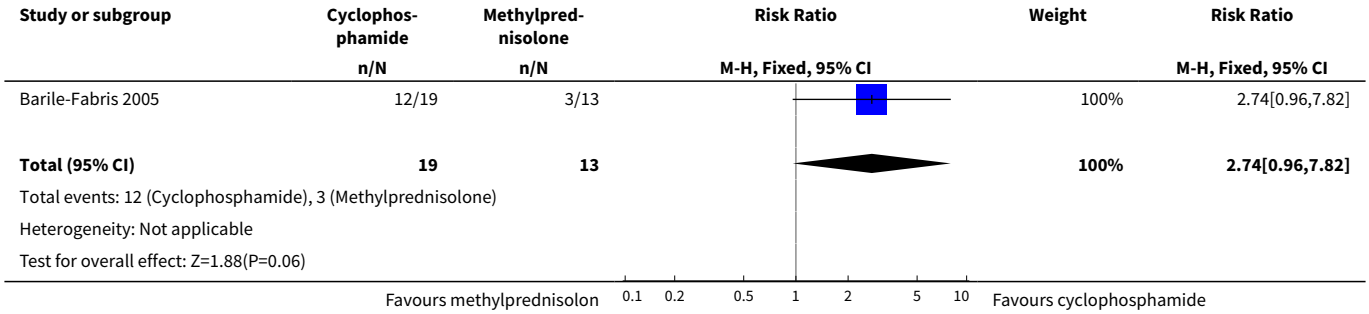


Analysis 1.6. Comparison 1 Cyclophosphamide versus methylprednisolone, Outcome 6 Adverse events.





Analysis 1.7. Comparison 1 Cyclophosphamide versus methylprednisolone, Outcome 7 Completion of the protocol after 2 years.



APPENDICES

Appendix 1. CENTRAL (*The Cochrane Library*) search strategy

#1 MeSH descriptor Lupus Erythematosus, Systemic explode all trees

#2 lupus next erythematosus:ti,ab

#3 sle:ti,ab

#4 (#1 OR #2 OR #3)

#5 MeSH descriptor Cyclophosphamide explode all trees

#6 cyclophosph*:ti,ab

#7 cytophosphan:ti,ab

#8 cytoxan:ti,ab

#9 sendoxan:ti,ab

#10 endoxan:ti,ab

#11 neosar:ti,ab

#12 nsc-26271:ti,ab

#13 procytox:ti,ab

#14 b-518:ti,ab

#15 ifosfamide:ti,ab

#16 iso endoxan:ti,ab

#17 isophosphamide:ti,ab

#18 iphosphamide:ti,ab

#19 isofosfamide:ti,ab

#20 holoxan:ti,ab

#21 nsc-109*:ti,ab

#22 "asta z 4942":ti,ab

#23 cfx:ti,ab

#24 phosphoramide next mustard*:ti,ab

#25 (#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24)

#26 (#4 AND #25)

#27 MeSH descriptor Methylprednisolone explode all trees

#28 methylprednis*:ti,ab

#29 metipred:ti,ab

#30 urbason:ti,ab

#31 medrol:ti,ab

#32 medrone:ti,ab

#33 adv?ntan:ti,ab

#34 (#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33)

#35 (#26 AND #34)#

Appendix 2. MEDLINE search strategy

1. exp Lupus Erythematosus, Systemic/

2. lupus erythematosus.tw.

3. sle.tw.

4. or/1-3

5. exp Cyclophosphamide/

6. cyclophosph$.tw.

7. cytophosphan.tw.

8. cytoxan.tw.

9. sendoxan.tw.

10. endoxan.tw.

11. neosar.tw.

12. nsc-26271.tw.

13. procytox.tw.

14. b-518.tw.

15. ifosfamide.tw.

16. iso endoxan.tw.

17. isophosphamide.tw.

18. iphosphamide.tw.

19. isofosfamide.tw.

20. holoxan.tw.

21. nsc-109$.tw.

22. asta z 4942.tw.

23. cfx.tw.

24. phosphoramide mustard$.tw.

25. or/5-24

26. 4 and 25

27. exp Methylprednisolone/

28. methylprednis$.tw.

29. metipred.tw.

30. urbason.tw.

31. medrol.tw.

32. medrone.tw.

33. adv?ntan.tw.

34. or/27-33

35. 26 and 34

Appendix 3. EMBASE search strategy

1. exp lupus erythematosus/

2. lupus erythematosus.tw.

3. sle.tw.

4. or/1-3

5. cyclophosphamide/

6. cyclophosph$.tw.

7. cytophosphan.tw.

8. cytoxan.tw.

9. sendoxan.tw.

10. endoxan.tw.

11. neosar.tw.

12. nsc-26271.tw.

13. procytox.tw.

14. b-518.tw.

15. ifosfamide.tw.

16. iso endoxan.tw.

17. isophosphamide.tw.

18. iphosphamide.tw.

19. isofosfamide.tw.

20. holoxan.tw.

21. nsc-109$.tw.

22. asta z 4942.tw.

23. cfx.tw.

24. phosphoramide mustard$.tw.

25. or/5-24

26. methylprednisolone/

27. methylprednis$.tw.

28. metipred.tw.

29. urbason.tw.

30. medrol.tw.

31. medrone.tw.

32. adv?ntan.tw.

33. or/26-32

34. and/4,25,33

35. 2010$.em.

36. 34 and 35

Appendix 4. LILACS search strategy

lupus erythematosus OR SLE (in words)

AND

Cyclophosphamide (in words)

AND

Methylprednisolone (in words)

Appendix 5. Scopus search strategy

#1 (TITLE-ABS-KEY(lupus erythematosus OR SLE))

#2 (TITLE-ABS-KEY(cyclophosphamide))

#3 (TITLE-ABS-KEY(methylprednisolone))

#4 #1 AND #2 AND #3

#5 #4 LIMIT-TO PUBYEAR 2005 to 2012 AND Conference Paper as document type

Appendix 6. WHO International Clinical Trials Registry Platform

lupus erythematosus OR SLE (in condition)

AND Cyclophosphamide AND Methylprednisolone (in intervention)

WHAT'S NEW

Date	Event	Description
12 December 2012	New citation required but conclusions have not changed	We updated the methodology to include 'Risk of bias' and 'Summary of findings' tables.
12 December 2012	New search has been performed	This is a second update (an update of the 2006 version). We conducted a new search but no studies were added to the review.

HISTORY

Protocol first published: Issue 1, 1999
Review first published: Issue 3, 2000

Date	Event	Description
8 September 2008	New search has been performed	Converted to new review format. CMSG ID C024-R.
21 February 2006	New citation required and conclusions have changed	This updated version contains one new randomised controlled trial. The original version of this review did not have any included trials.

CONTRIBUTIONS OF AUTHORS

Conceiving the review: VFMT, AAC
Designing the review: VFMT, AAC, ANA

Co-ordinating the review: VFMT, AAC, ANA
Developing the search strategy: AAC
Undertaking searches: VFMT, AAC, JFNN
Screening search results: VFMT, AAC
Organising retrieval of papers: VFMT
Screening retrieved papers against inclusion criteria: VFMT, RM
Appraising quality of papers: VFMT, AAC, RM
Abstracting data from papers: VFMT, AAC
Data management for the review
Entering data into RevMan: VFMT
Analysis of data: VFMT, AAC
Interpretation of data: VFMT
Providing a methodological perspective: VFMT, AAC
Providing a clinical perspective: VFMT, AAC
Providing a policy perspective: VFMT, AAC
Writing the review: VFMT, AAC

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Clinical Trials and Meta-analysis Unit, Federal University of São Paulo, Brazil.
- Universidade Santo Amaro, Brazil.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Cyclophosphamide [*therapeutic use]; Immunosuppressive Agents [*therapeutic use]; Lupus Erythematosus, Systemic [*complications] [drug therapy]; Methylprednisolone [*therapeutic use]; Neurocognitive Disorders [*drug therapy] [etiology]; Neuroprotective Agents [*therapeutic use]; Randomized Controlled Trials as Topic; Seizures [drug therapy] [etiology]

MeSH check words

Humans